

Special topic

Carmen Nájera* and José Miguel Sansano

Synthesis of pyrrolizidines and indolizidines by multicomponent 1,3-dipolar cycloaddition of azomethine ylides

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Abstract: Different multicomponent 1,3-dipolar cycloadditions (1,3-DC) of cyclic α -amino acid derivatives with aldehydes and dipolarophiles have been described as efficient and simple methodologies for the synthesis of the pyrrolidine unit of pyrrolizidines and indolizidines. When free cyclic α -amino acids are used, a thermal promoted decarboxylative process generates *in situ* the corresponding non-stabilized azomethine ylides, which afforded the corresponding pyrrolizidines and indolizidines with a hydrogen in the bicyclic units. This methodology has been employed to the synthesis of complex systems including spiro derivatives when ketones are used as carbonyl component. In addition, working with cyclic α -amino acid derived esters, the three-component 1,3-DC takes place under milder reaction conditions giving the corresponding pyrrolizidines and indolizidines with an alkoxycarbonyl group in the bridge adjacent carbon to the nitrogen. This methodology can be carried out by a double consecutive or stepwise 1,3-DC to provide pyrrolizidines via the precursor prolinates. The conformation of the azomethine ylide controls the endo/exo diastereoselectivity of the 1,3-DC.

Keywords: 1,3-dipolar cycloadditions; azomethine ylides; carbonyl compounds; Distinguished Women in Chemistry and Chemical Engineering; electrophilic alkene; iminium ions; indolizidines; multicomponent reactions; pyrrolizidines.

Introduction

Natural and non-natural pyrrolizidine [1] and indolizidine [2] alkaloids show important biological properties especially polyhydroxylated systems, which are potentially glycosidase inhibitors and have antibacterial, antitumor, antiviral, anti-inflammatory and immunostimulatory properties (Fig. 1). For these reasons many synthetic strategies have been described being the intermolecular three-component 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylides the most efficient approach for the generation of the common pyrrolidine unit in a single reaction step [3–6]. This multicomponent reaction (MCR) involves the formation of a dipole formed by an iminium anion adjacent to a carbanion, by reaction of a cyclic amino acid with a carbonyl compound, which is trapped by a dipolarophile. This 1,3-DC can take place through two strategies depending on the amino acid derivative: (a) starting from the free amino acid, and (b) from the amino ester (Scheme 1). In the first case, a decarboxylative condensation occurs with the formation of a non-stabilized azomethine ylide, whereas in the second case a stabilized azomethine ylide is involved. Usually, the first multicomponent

***Corresponding author: Carmen Nájera**, Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, Apdo. 99, Alicante 03080, Spain, e-mail: cnajera@ua.es

José Miguel Sansano: Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, Apdo. 99, Alicante 03080, Spain; and Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, Alicante 03080, Spain

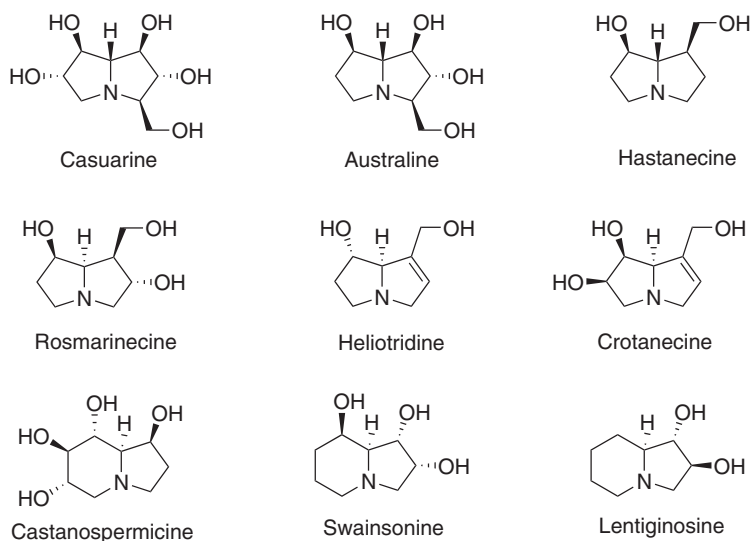
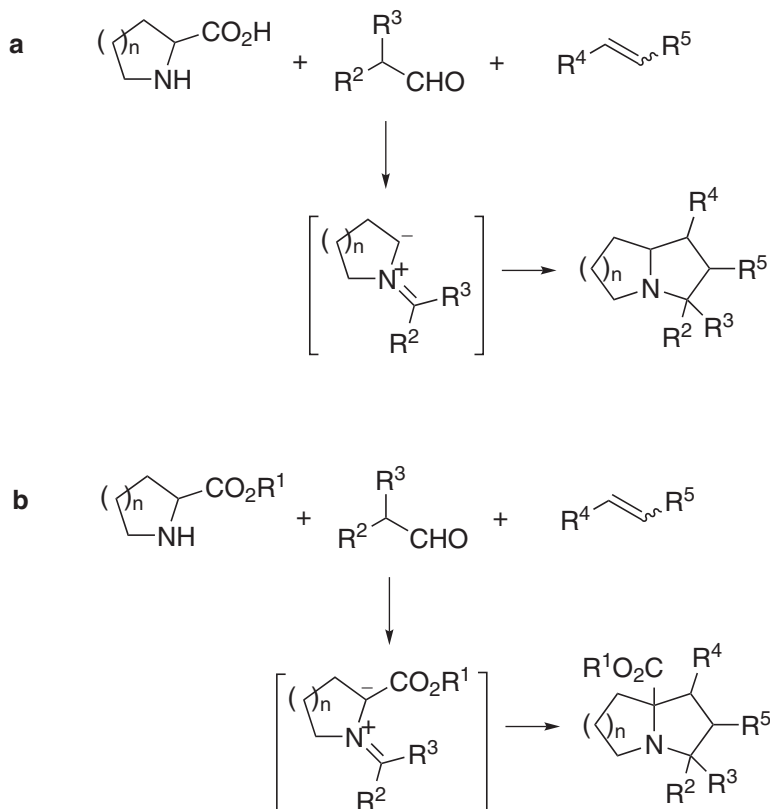


Fig. 1: Selected pyrrolizidine and indolizidine alkaloids.

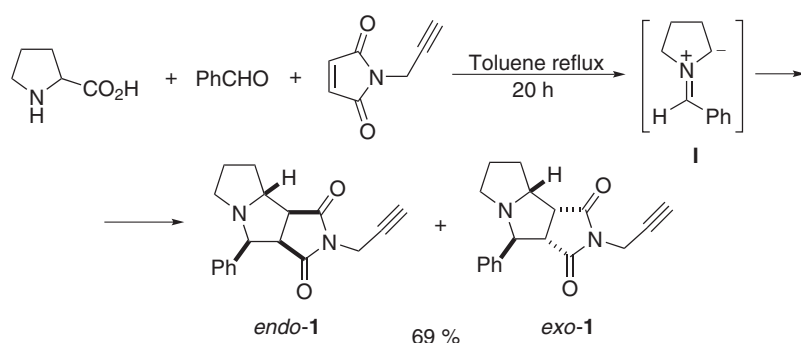
reaction must be performed under heating, where the second one needs milder reaction conditions. In this minireview, we highlight the development of intermolecular MCR 1,3-DC of azomethine ylides focused to the synthesis of pyrrolizidines and indolizidines including our contributions in this field, covering from its origin to recent contributions.



Scheme 1: Strategies for three-component 1,3-DC.

Multicomponent synthesis of pyrrolizidines by decarboxylative 1,3-DC

Since the pioneering work of Grigg and co-workers [7] the decarboxylative routes of azomethine ylides has been widely used in 1,3-DC. This process can involve an intermediate oxazolidin-5-one, which loses carbon dioxide in a 1,3-dipolar cycloreversion reaction generating the non-stabilized azomethine ylide, but also by a 1,4-protropic rearrangement of the azomethine ylide [8–10]. The groups of Grigg et al [9, 10] and Orsini et al [11] described the synthesis of pyrrolizidines by MCR of proline with aldehydes and electrophilic olefins leading to mixtures of diastereomers. For instance, using benzaldehyde and *N*-propargyl maleimide under toluene reflux for 20 h a 3:1 mixture of *endo/exo* pyrrolizidines **1** were obtained via the *anti*-dipole **I** (Scheme 2) [12].



Scheme 2: Multicomponent 1,3-DC of proline, benzaldehyde and *N*-propargyl maleimide.

Further applications of this process are depicted in Fig. 2. A four-component reaction of nihydrin, 1,2-phenylenediamine, proline and *N*-aryl maleimides gave after microwave (MW) irradiation (3–5 min at 600 W) *exo*-spiropyrrolizidines **2** in 85–95 % yield through intermediacy of azomethine ylide **II** [13]. Dispiroindeno-quinoxaline-pyrrolizidine derivatives **3–6** have been prepared by subsequent *in situ* reaction of nihydrin with 1,2-phenylenediamine, then addition of L-proline and as carbonyl component: 2-arylidene-1,3-indanone, (*E*)-2-arylidene-tetrahydronaphthalene-1-ones, (*E*)-3-arylidene-4-chromanones and (*E*)-2-oxoindolino-3-ylidene acetophenones using 20 mol % of heteropolyacid $H_4[Si(W_{30}O_{10})_3]$ -silica as catalyst in acetonitrile [14]. The same group described the synthesis of spiroheterocycles **7** by a three-component, under solvent free MW irradiation of proline, nihydrin and 9-arylidene-fluorenes in high yields by means of azomethine ylides **III** derived from nihydrin [15]. Other spiro derivatives **8–10** (Fig. 2) have been synthesized using as cyclic ketones nihydrin, 11*H*-indeno[1,2-*b*]quinoxalin-11-one and acenaphthenequinone, respectively, being azomethine ylides **II–IV** the corresponding intermediates [16].

Azomethine ylides derived from acenaphthenequinone **IV** and isatins **V** were the intermediates in the three-component 1,3-DC with a carbohydrate derived olefin providing spiro cycloadducts **11** and **12**, respectively (Scheme 3) [17].

Perumal and co-workers [18] have described the three-component 1,3-DC of proline with acenaphthenequinone and α,α' -bisalkylidenepyridinones under refluxed methanol affording spiropyrido-pyrrolizidines **13** in high yields (Fig. 2). Acenaphthenequinone has been allowed to react with proline and (*E*)-2-oxoindolino-3-ylidene acetophenones using MW irradiation and mediated by $ZrOCl_2 \cdot 8H_2O$ giving mainly products **14** [19] (Fig. 2). Nihydrin has been used as carbonyl component in the synthesis of spiropyrrolizidines **15** and **16** in the presence of chalcones and nitrostyrenes, respectively in methanol at rt [20] (Fig. 2). Korotaev and co-workers used 3-nitro-2*H*-chromenes as dipolarophiles leading to the formation of the corresponding spiropyrrolizidines **17** in good yields upon heating in ethanol [21] (Fig. 2).

Isatins have been widely used as carbonyl component for the multicomponent synthesis of spirooxindole-pyrrolizidines with potential biological activity using proline and different dipolarophiles. Raghunathan

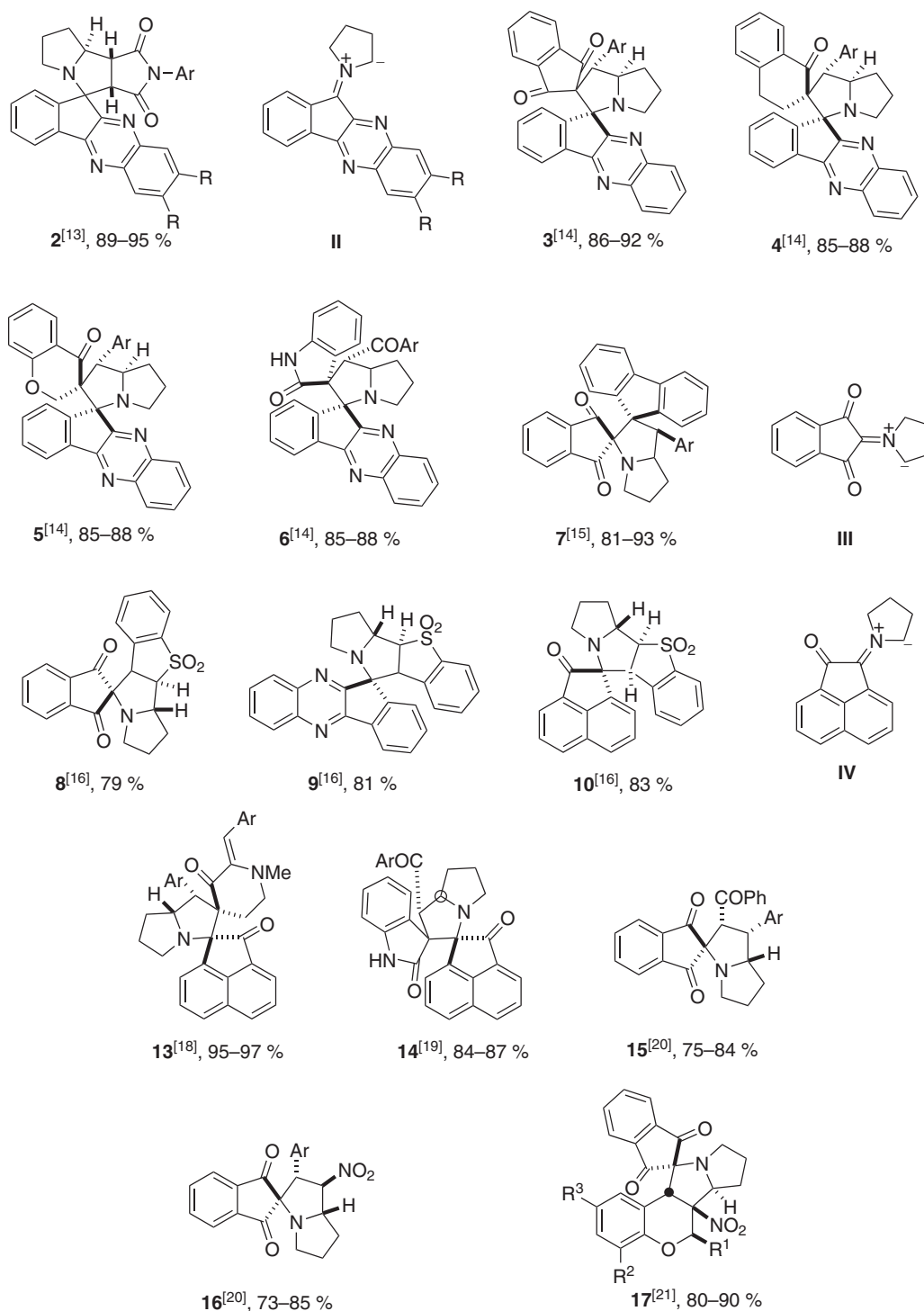
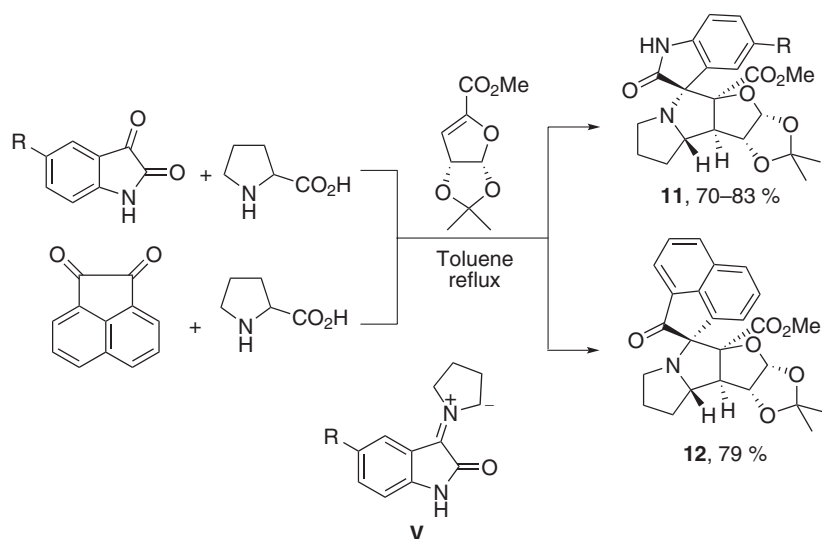


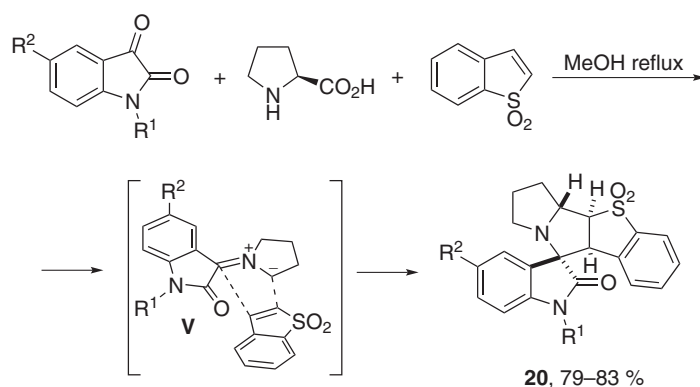
Fig. 2: Spiro-fused pyrrolizidines and azomethine ylides.

and co-workers firstly described the MCR of isatin with proline and 9-arylidene-fluorene in a solvent-free MW assisted 1,3-DC affording the corresponding dispiro-oxindole-pyrrolizidines in very good yields **18** [22] (Fig. 3). Working under ultrasonication in the presence of silica as a catalyst dispiro-oxindole-pyrrolizidines **19** were formed using alkylidene-oxindoles as dipolarophile in acetonitrile [23] (Fig. 3). These reaction conditions were applied to the same MCR using nihydrin as carbonyl component. In the case of spirooxindoles



Scheme 3: Three-component 1,3-DC of proline with isatins or acenaphthenequinone and a sugar-derived olefin.

20 the pyrrolizidine unit has been prepared using benzo[*b*]thiophene dioxide under refluxing methanol for 45–110 min [16]. In this case the azomethine ylide **V** is participating giving only one regioisomer through the approach represented in Scheme 4.



Scheme 4: Three-component 1,3-DC of isatins, proline and benzo[*b*]thiophene dioxide.

For the synthesis of spirooxindoles **21** the sugar-derived α,β -unsaturated lactones were employed as dipolarophiles under refluxing toluene by intermediacy of azomethine ylide **V** [24] (Fig. 3). Glyco-3-nitrochromenes **22** have been used as dipolarophiles by the same group in the MCR of isatin and proline under refluxing acetonitrile affording pyrrolidinyl spirooxindoles **23** [25] (Fig. 3). They also employed acenaphthalenones and indenoquinoxalines as carbonyl components affording the corresponding glycol 3-nitrochromane hybrid pyrrolizidinyl spiro-derivatives in 81–84 % yield. Babu and co-workers have employed the Diels-Alder cycloadduct **24**, derived from furan and methyl maleate, as dipolarophile in the three-component 1,3-DC of isatins and proline under refluxing ethanol or in a mixture of ethanol and 1,4-dioxane. The resulting norbornane-fused spirooxindolo-pyrrolizidines **25** were obtained in moderate yields [26] (Fig. 3). When (*E*)-3-benzylidenechroman-2-ones **26** were used as dipolarophiles the corresponding dispirooxindole-pyrrolizidines **27** were obtained under refluxing toluene in high yields [27] (Fig. 3). Yang and co-workers have used 1-benzyl-3-acetylidenexindole **28** as dipolarophile for the three-component 1,3-DC of *N*-benzylisatin and proline. The reaction took place at rt in methanol providing the dispirooxindole derivative **29** in high yield [28] (Fig. 3). The cycloadducts **30**, derived from β -nitrostyrene, have been prepared from isatins and L-proline as well as

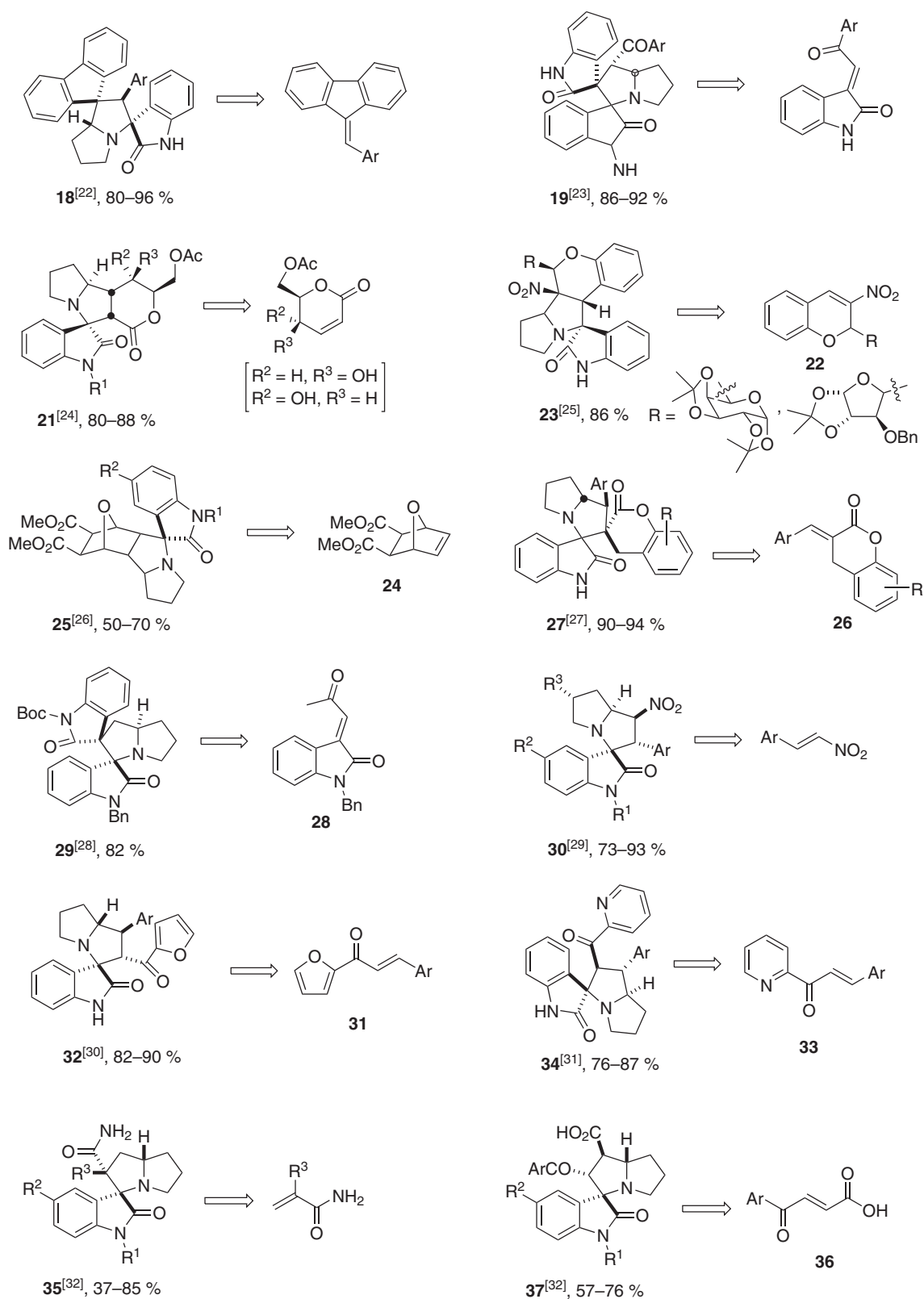


Fig. 3: Spirooxindole-pyrrolizidines.

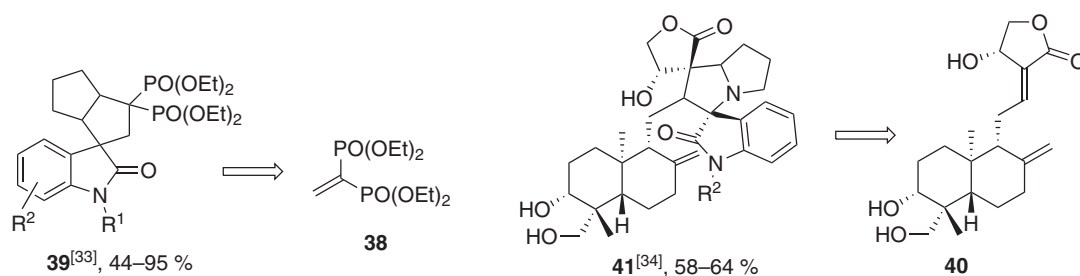
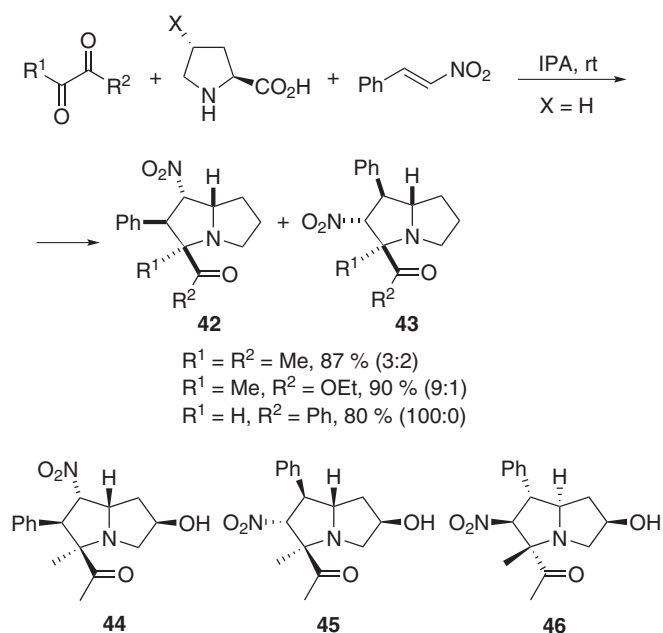


Fig. 3: (Continued)

(4S)-4-hydroxy-L-proline in a mixture of propylene carbonate and water as solvents at 90 °C in very good yields [29] (Fig. 3). From LC₅₀ toxicity assays in zebrafish embryos, three molecules were identified as the most hepatotoxicity derivatives. By using α,β -unsaturated ketones **31** as dipolarophiles, the three-component 1,3-DC of isatin and proline afforded products **32** in very good yields [30] (Fig. 3). These spirooxindoles **32** bearing the furanyl moiety displayed good *in vitro* antibacterial activity against Gram-negative bacteria, especially compound **32** with Ar = MeOC₆H₄. Under refluxing methanol, a library of spirooxindole-pyrrolizidine derivatives **34** have been prepared in a MCR using enones **33** as dipolarophiles in good yield [31] (Fig. 3). Spirooxindole-pyrrolizidines **35** and **37** were obtained using acrylamides and aroyl acrylic acid **36** as dipolarophiles, respectively [32] (Fig. 3). These MCR were performed in refluxing aqueous methanol (1:3) in moderate to good yield in the case of compounds **35** and at rt for products **37**. Montmorillonite has been used as a catalyst (10 mol %) for the 1,3-DC of isatins, proline and tetraethylvinylidenebis(phosphonate) (**38**) leading to mixture of spirooxindole-pyrrolizidines **39** in moderate to good yields [33] (Fig. 3). The andrographolide adducts **41** have been prepared under refluxing aqueous methanol (9:1) in moderate yields using angrapholide **40**, the major labdane diterpene constituent of the medicinal plant *Andrographis paniculate*, as dipolarophile [34] (Fig. 3).

The MCR of acyclic 1,2-dicarbonyl derivatives, such as butane-2,3-dione and ethyl pyruvate, with L-proline and β -nitrostyrene in isopropanol (IPA) at rt gave the corresponding pyrrolizidines **42** and **43** as a mixture of regioisomers (Scheme 5) [35]. However, in the case of phenylglyoxal only product **42** was formed. On the

Scheme 5: Three-component 1,3-DC of 1,2-dicarbonyl compounds, prolines and β -nitrostyrene.

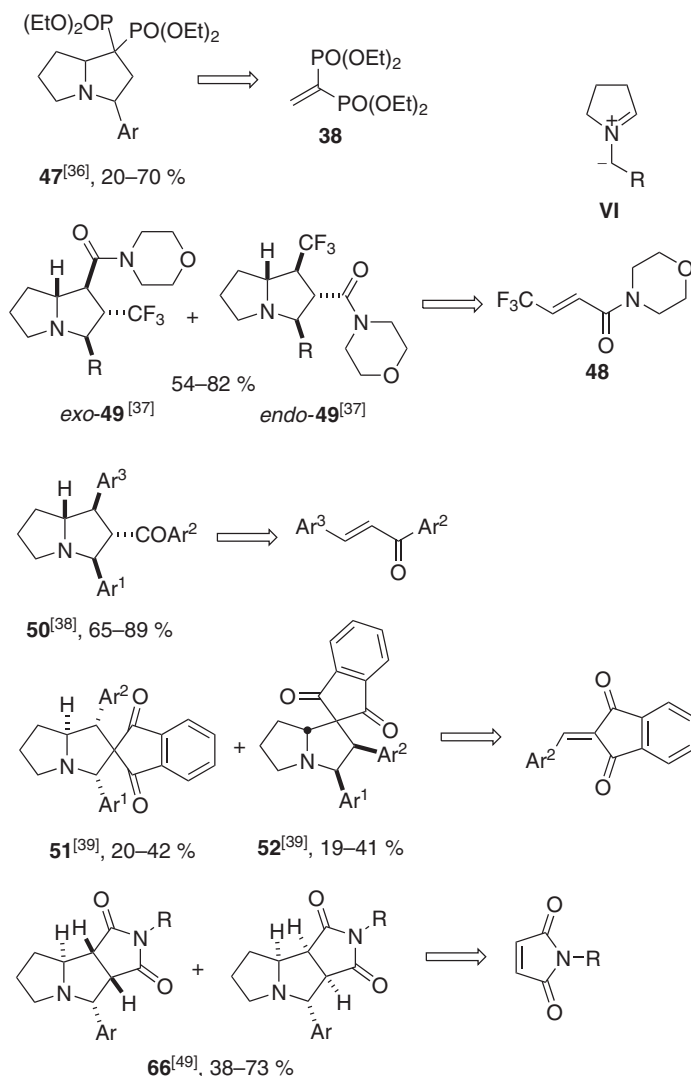


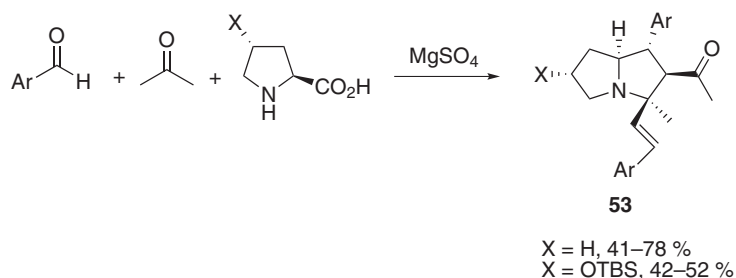
Fig. 4: Pyrrolizidines from L-proline, aldehydes and dipolarophiles.

other hand, (4*S*)-4-hydroxy-L-proline reacted with butane-2,3-dione giving a 1:4:1 mixture products **44**:**45**:**46**, respectively, in 78 % overall yield.

Wu and co-workers used tetraethyl vinylbis(phosphonate) (**38**) in the three-component 1,3-DC of proline with benzaldehydes in toluene at 80 °C catalyzed by cerium(IV) oxide (5 mol %) leading regioselectively to pyrrolizidines **47** in moderate yields [36] (Fig. 4). Trifluoromethylated pyrrolizidines **49** have been synthesized by reaction of aldehydes, proline and β -trifluoromethyl acrylamides **48** in DMSO at 80 °C [37] (Fig. 4). Moderate regioselectivity (up to 1:6) was observed and excellent diastereoselectivity (>20:1) arose for compounds **49**, being the *anti*-azomethine ylide **VI** the most stable intermediate according to DFT calculations.

When chalcones were employed as dipolarophiles in dry DMF at 90 °C, *endo*-adducts **50** were obtained with excellent regio- and diastereoselectivity [38] (Fig. 4). However, oxazolidines were also formed by reaction of proline with 2 eq. of aldehyde. Both compounds were isolated in 65–89 % overall yields. The MW-promoted (275 °C, 300 W) three-component 1,3-DC of proline, aromatic aldehydes and 2-arylmethyleneindene-1,3-dione in 1,4-dioxane provided spiropyrrolizidines **51** and **52** in moderate yields [39] (Fig. 4).

The one-pot sequence aldol condensation of acetone with aldehydes catalyzed by proline, followed by 1,3-DC of the α,β -unsaturated ketone with proline, afforded racemic pyrrolizidines **53** ($\text{X}=\text{H}$) in moderate

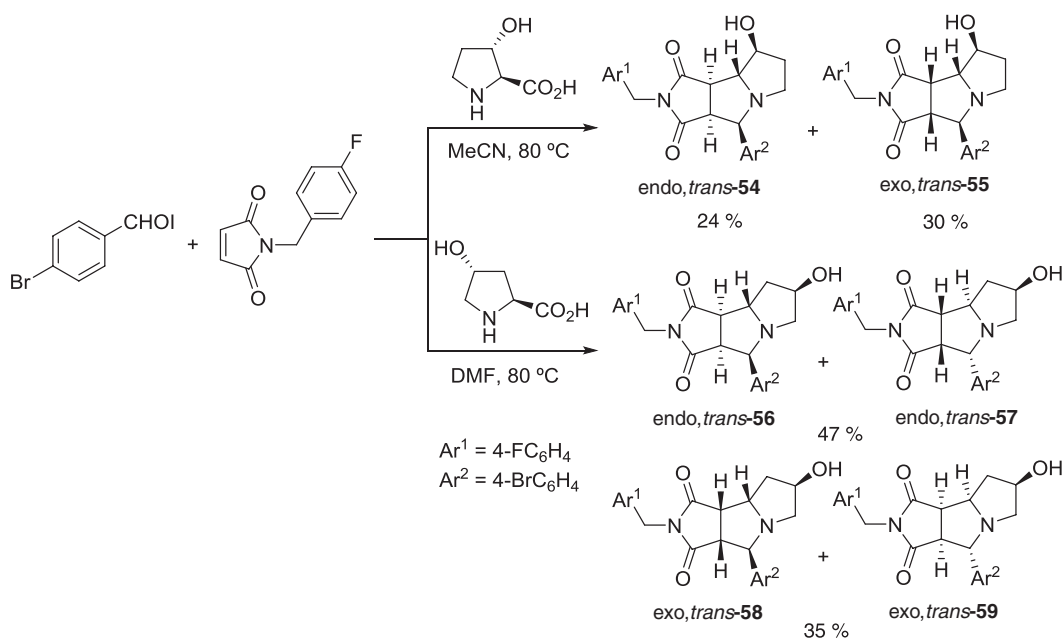


Scheme 6: Three-component 1,3-DC of aldehydes, acetone and prolines.

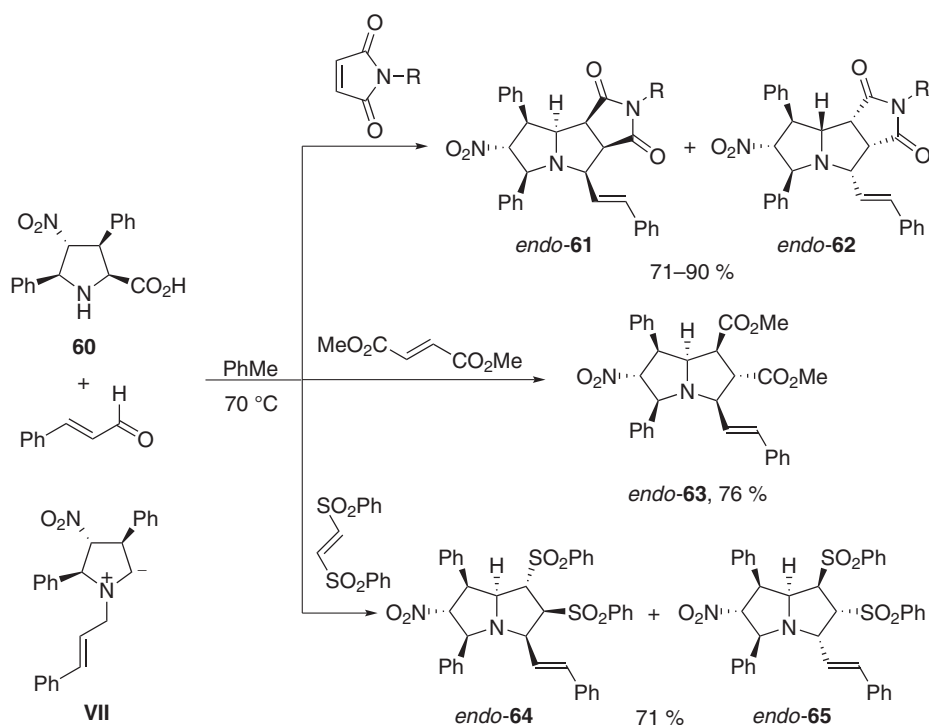
yields (Scheme 6) [40]. The reaction was performed in the presence of 10 mol % of MgSO_4 in DMSO at rt. Silylated (4*S*)-4-hydroxy-L-proline lead to the formation of enantiopure products **53** (X = OTBS) in moderate yields.

Diederich and co-workers have prepared several tricyclic thrombin inhibitors by using a decarboxylative 1,3-DC of prolines with benzaldehydes and maleimides [41–46]. The most active were those derived from *trans*-3-hydroxy-L-proline or *trans*-4-hydroxy-L-proline with 4-bromobenzaldehyde and *N*-(4-fluorobenzyl)maleimide as the key step (Scheme 7) [45, 46]. In the first case, the 1,3-DC was performed in MeCN at 80 °C for 18 h, affording a mixture of separable enantiopure products *endo,trans*-**54** and *exo,trans*-**55** in 24 and 30 %, respectively. The same process with *trans*-4-hydroxy-L-proline in DMF at 80 °C for 48 h, provided two pairs of inseparable diastereomers, that means, a mixture 1:1 of *endo*-products **56** and **57** together with a mixture of *exo*-products **58** and **59**. The desired product **56** was further isolated after several transformations.

Our group has recently prepared enantiopure nitropyrrolizidines **61–65** from chiral *exo*-4-nitroproline **60** [47], aldehydes and dipolarophiles (Scheme 8) [48]. These three-component 1,3-DC took place in toluene at rt or 70 °C, depending on the dipolarophile, affording mixtures of diastereomers with de up to >99 %. In the case of cinnamaldehyde and *N*-methyl or *N*-phenyl maleimides, pyrrolizidines *endo*-**62** were mainly obtained, whereas *N*-(4-bromophenyl)maleimide gave exclusively compound **61** in 80 % yield. Dimethyl



Scheme 7: Three-component 1,3-DC of 4-bromobenzaldehyde, *N*-(4-fluorobenzyl)-maleimide and (3*S*)- and (4*S*)-hydroxy-L-prolines.

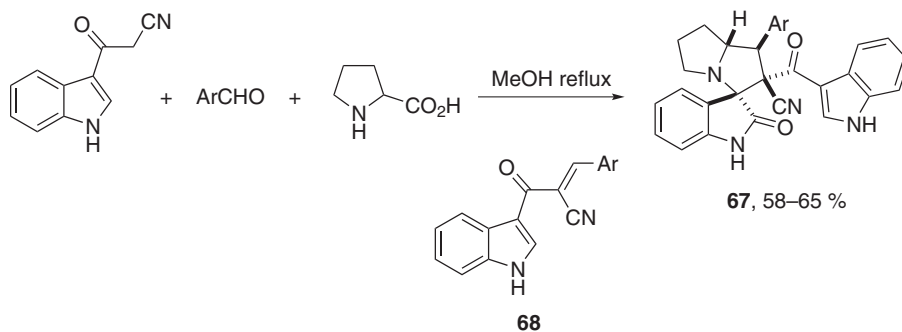


Scheme 8: Multicomponent 1,3-DC of cinnamaldehyde, nitroproline **60** and dipolarophiles.

fumarate also provided exclusively *endo*-**63** and (*E*)-bis(phenylsulfonyl)ethylene gave a 2:1 mixture of **64** and **65**. Other aldehydes, such as benzaldehyde and 3-phenylpropanal, provided compounds **61** and **62** in modest yield (23–47 %). In these cases, the *endo*-selectivity was due to the participation of azomethine ylide **VII**.

A different multicomponent 1,3-DC has been described by Sridharan and co-workers [49] using benzylic alcohols instead of aldehydes. This reaction must be carried out under Ir catalysis, so a hydrogen autotransfer generated *in situ* the corresponding aldehyde, which by reaction with proline and maleimide, afforded a *ca.* 1:1 mixture of pyrrolizidines **66** (Fig. 4).

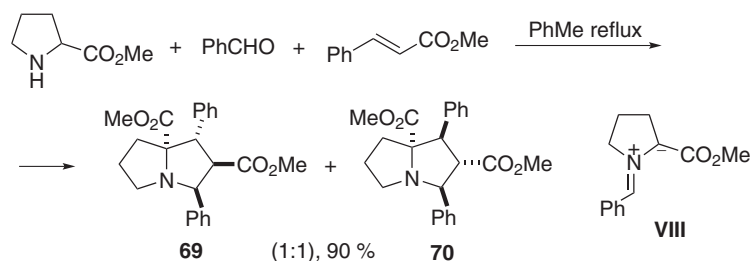
A four-component procedure has been carried out with isatin, proline, 3-(cyanoacetyl)indole and aldehydes under refluxing methanol affording spiropyrrolizidines **67** in moderate yields (Scheme 9) [50]. The corresponding dipolarophiles **68** were formed *in situ* via a Knoevenagel condensation between 3-(cyanoacetyl)indole and aldehydes.



Scheme 9: Four-component 1,3-DC of isatin, proline, 3-(cyanoacetyl)indole and aldehydes.

Multicomponent synthesis of pyrrolizidines by 1,3-DC

Alkyl proline derivatives gave stabilized azomethine ylides by reaction with carbonyl compounds, which can be trapped by dipolarophiles giving substituted pyrrolizidines. Joucla and co-workers have described the three-component 1,3-DC of methyl proline with benzaldehyde and methyl (*E*)-cinnamate in refluxing toluene giving, regioselectively, a 1:1 mixture of pyrrolizidines **69** and **70** in 90 % yield (Scheme 10) [51]. The relative configuration of compounds **69** and **70** can be attributed to the formation of the azomethine ylide **VIII**, which attacks to the dipolarophile by the α -position.



Scheme 10: Multicomponent 1,3-DC of methyl proline, benzaldehyde and methyl (*E*)-cinnamate.

The former process was performed by Maiti and co-workers [52] with cinnamaldehydes and different dipolarophiles, in dichloromethane at rt, providing pyrrolizidines **71** in high yields through an azomethine ylide of type **VIII**, by an *endo* approach (Fig. 5). When β -nitrostyrenes were used as dipolarophiles, compounds **72** were regio- and diastereoselectively formed according to an *endo*-approach and similar behavior was observed with acrylates and acrylonitrile leading to products **73** in good yields (Fig. 5). Independently, our group studied the same multicomponent 1,3-DC between methyl proline hydrochloride in the presence of Et_3N , using toluene as solvent at rt, different aldehydes and dipolarophiles [53]. This process can be performed alternatively in the presence of AgOAc (5 mol %) affording similar results. The presence of AgOAc was crucial when benzaldehyde and isopentanal were allowed to react with methyl acrylate as dipolarophile

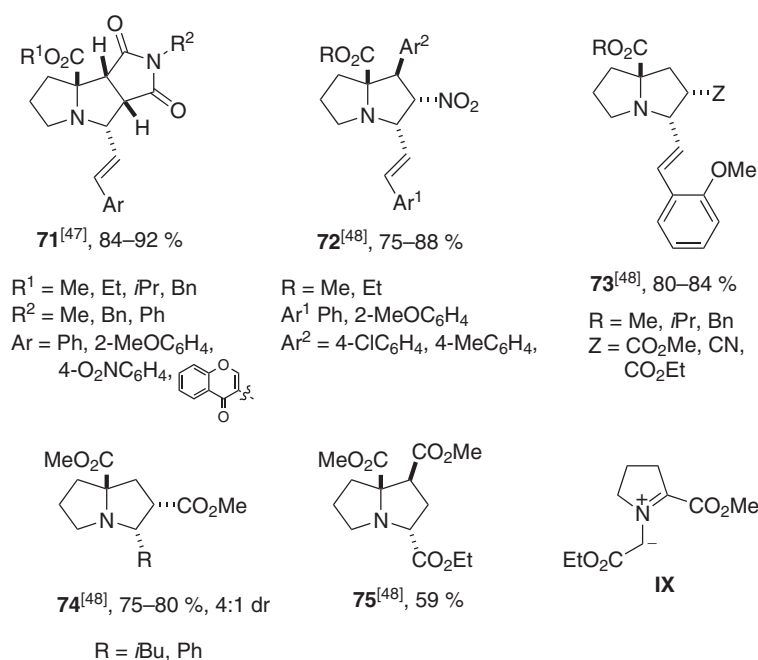
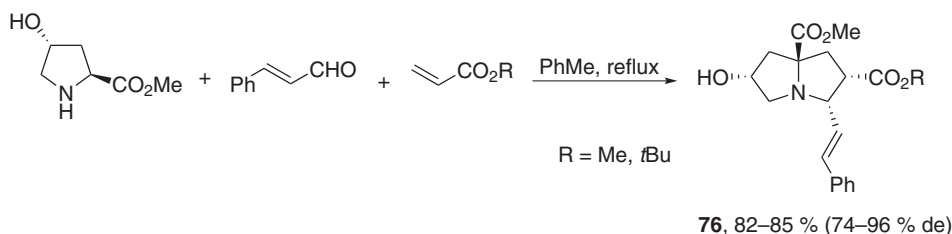


Fig. 5: Pyrrolizidines from alkyl prolinates, aldehydes and dipolarophiles.

giving mainly products **74** with up to 99:1 dr (Fig. 5). However, when ethyl glyoxylate was used as aldehyde the reaction only occurred in the presence of AgOAc affording exclusively the other regioisomer **75** as the only diastereomer. The formation of **75** can be explained by the participation of the azomethine ylide **IX**, which reacted by the less substituted γ -position (Fig. 5).

Methyl (4*S*)-4-hydroxyprolinate gave mainly the corresponding enantiomerically pure adducts **76** when cinnamaldehyde and acrylates were used working under refluxing toluene (Scheme 11) [48].



Scheme 11: Three-component 1,3-DC of methyl (4*S*)-4-hydroxyprolinate with cinnamaldehyde and acrylates.

However, working in the presence, or in the absence of AgOAc, and *N*-methylmaleimide as dipolarophile, a 3:1 mixture of diastereomeric adducts **77** and **78** were obtained [54] (Fig. 6). Further studies about these processes, performed by our group with methyl (4*S*)-4-hydroxyprolinate, benzaldehyde and *tert*-butyl acrylate indicated that only compound **79** was isolated in the absence of AgOAc in 75 % yield. In the case of using (*E*)-1,2-bis(phenylsulfonyl)ethylene, also the corresponding *endo*-pyrrolizidine **80** was exclusively obtained (Fig. 6) [54]. When *N*-crotonoyloxazolidinone was used as dipolarophile with methyl (4*S*)-4-hydroxyprolinate and cinnamaldehyde product **81** was obtained in 90 % de (Fig. 6). From DFT calculations it can be deduced that the equilibrium between S-shape **X** and U-shape **XI** dipoles, derived from methyl prolinate and methyl (4*S*)-4-hydroxyprolinate and cinnamaldehyde, requires an activation barrier higher than 30 Kcal·mol^{−1} (Fig. 6). On the other hand, the high observed diastereoselection with the methyl (4*S*)-4-hydroxyprolinate derivative is a consequence of the presence of a hydrogen bonding during the *endo*-approach.

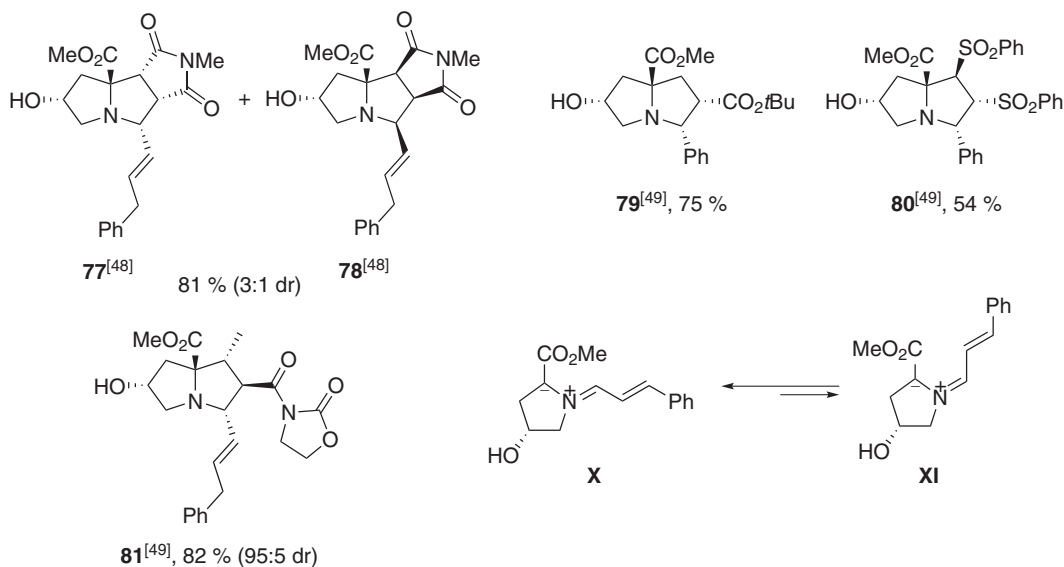
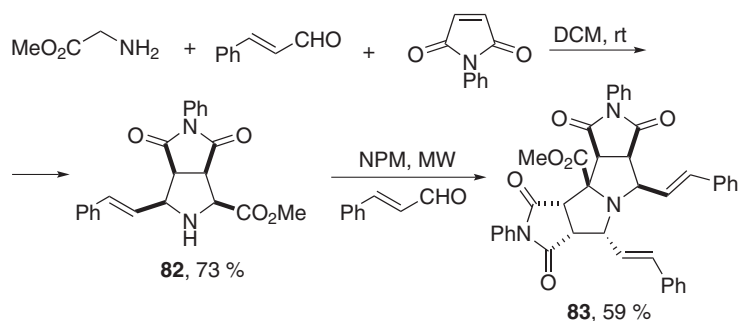


Fig. 6: Pyrrolizidines from methyl (4*S*)-4-hydroxyprolinate, aldehydes and dipolarophiles.

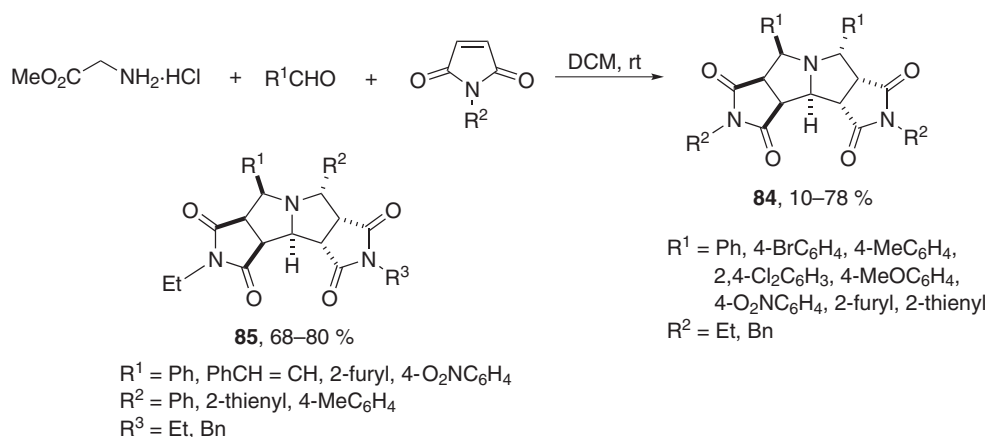
Consecutive three-component 1,3-DC were described by Shi and co-workers [55]. The initial multicomponent 1,3-DC was performed with glycine methyl ester, cinnamaldehyde and *N*-phenylmaleimide (NPM) giving racemic compound **82** in 73 % yield (Scheme 12). Further treatment of these adducts **82** with the same



Scheme 12: Consecutive multicomponent 1,3-DC.

reagents, under solvent-free conditions and heated with MW (700 W) for 10 min, afforded the tetracyclic product **83** in 59 % yield.

The same double 1,3-DC was performed by Zhang and co-workers in a single operation just under MW heating at 180 °C in toluene (Scheme 13) [56]. Different aldehydes and maleimides have been used giving products **84** in good yields. When the former process was performed stepwise, it means first the formation of compound **82** ($R^2 = \text{Et}$) and then different aldehydes and maleimides were added to the reaction media, the corresponding unsymmetrical tetracyclic compounds **85** were formed (Scheme 13).

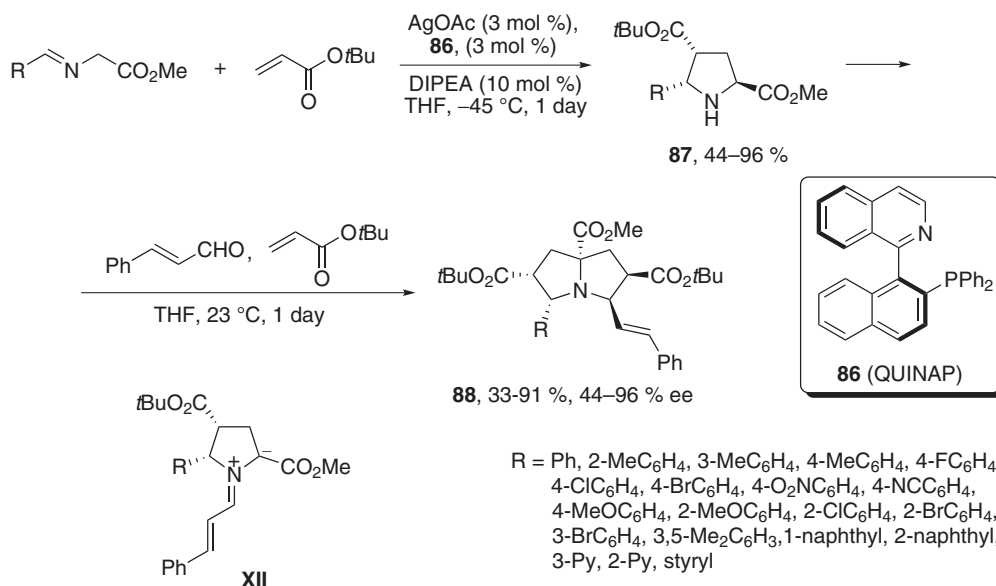


Scheme 13: Three-component 1,3-DC of methyl glycidate, aldehydes and maleimides.

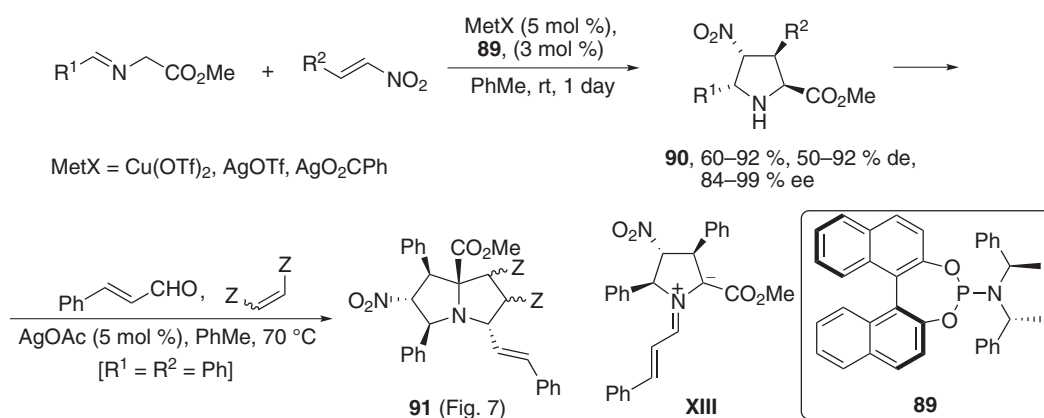
Reisman and co-workers [57] performed this double 1,3-DC, first by synthesizing prolines **87** in 44–96 % ee using Schreiber's conditions [58]. The 1,3-DC of glycine imino with *tert*-butyl acrylate using QUINAP (**86**) and AgOAc, as catalyst, provided prolinates **87** with ee up to 96 %. Without isolation of adducts **87**, cinnamaldehyde and *tert*-butyl acrylate were added to the reaction media at rt providing pyrrolizidines **88**, with the same ee that for **87** by intermediacy of the azomethine ylide **XII** (Scheme 14).

Our group has performed a double 1,3-DC using enantioenriched nitro prolinates **90** [59]. The first 1,3-DC was carried out with glycine imino esters and nitroalkenes using chiral phosphoramidite **89** and $\text{Cu}(\text{OTf})_2$ [60], AgOTf, or AgO_2CPh [42] complexes providing *exo*-4-nitroprolinates **90** [47, 60, 61]. Representative *exo*-**90** ($R^1 = R^2 = \text{Ph}$, >99 % ee) was allowed to react in a multicomponent 1,3-DC with cinnamaldehyde and different dipolarophiles under AgOAc catalysis in NMP at 70 °C affording pyrrolizidines *endo*- and *exo*-**91** in moderate to high diastereoselectivity by means of the azomethine ylide **XIII**, which reacts with dipolarophiles mainly through an *endo*-approach (Scheme 15 and Fig. 7) [59].

In the case of *N*-methylmaleimide or maleimide, the diastereomeric products **91a** and **91b** were obtained in 2:1 dr, which could be separated by flash chromatography. However, in the case of *N*-phenylmaleimide *exo*-**91c** was mainly obtained in a 3:1 dr which, after chromatographic separation, gave the *exo*-diastereomer in

**Scheme 14:** Double consecutive 1,3-DC.

65 % yield. Methyl acrylate gave regio- and diastereoselectively *endo*-**91d** in 92 % de which, after purification, afforded the pure pyrrolizidine in 88 % yield. Methyl fumarate gave a 2:1 mixture of *endo* and *exo*-**91e** which were separated after purification in 48 and 26 % yield, respectively. When methyl or ethyl acetylenedicarboxylates were employed as dipolarophiles compounds **91f** and **91g** were obtained in moderate yields. The *endo* approach could be explained by means of model **A** in which the steric interactions between the two phenyl groups of the *exo*-nitroproline **90** were avoided. In the case of *N*-phenylmaleimide (NPM) the steric interactions between the phenyl group of NPM and the nitro group favors the *exo*-approach as indicated in model **B**. On the other hand, the stereochemistry observed with the methyl acrylate justified the α -attack of the azomethine ylide **XIII** to the dipolarophile (Fig. 7).

**Scheme 15:** Double stepwise 1,3-DC.

Sing and co-workers has recently performed a double consecutive 1,3-DC by synthesizing firstly prolinates **93** by enantiocontrolled 1,3-DC of glycine imino esters with α,β -unsaturated pyrazolamides using the chiral complex formed by (*R*)-DM-SEGPHOS (**92**) and AgOTf (Scheme 16) [62]. Afterwards, cinnamaldehydes and maleimides were added to the reaction flask providing pyrrolizidines **94** in moderate to high *endo*-diastereoselectivity. Further reduction of compound *endo*-**94** with $NaBH_4$ and $LiAlH_4$ gave different hydroxylated pyrrolizidines.

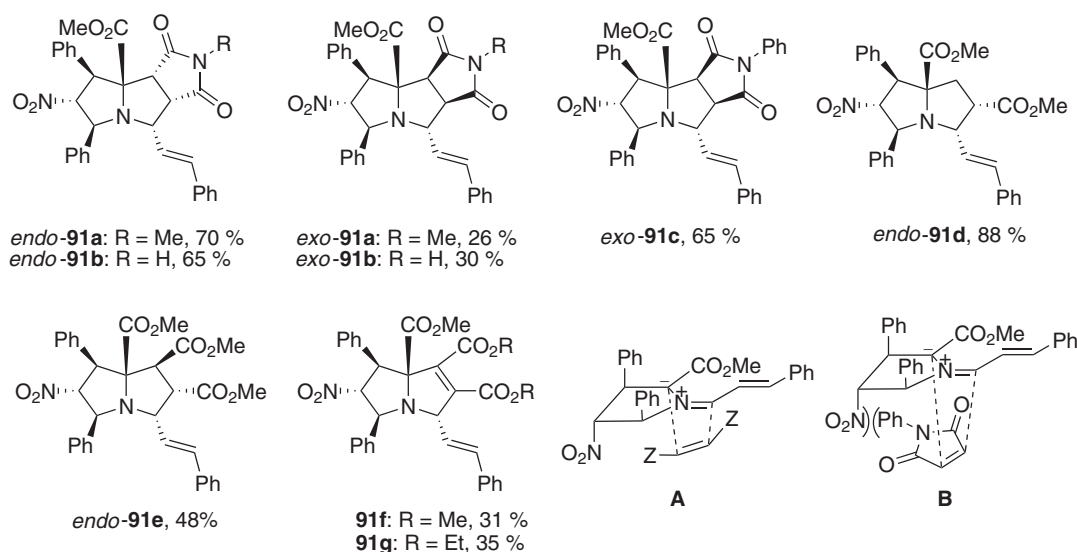
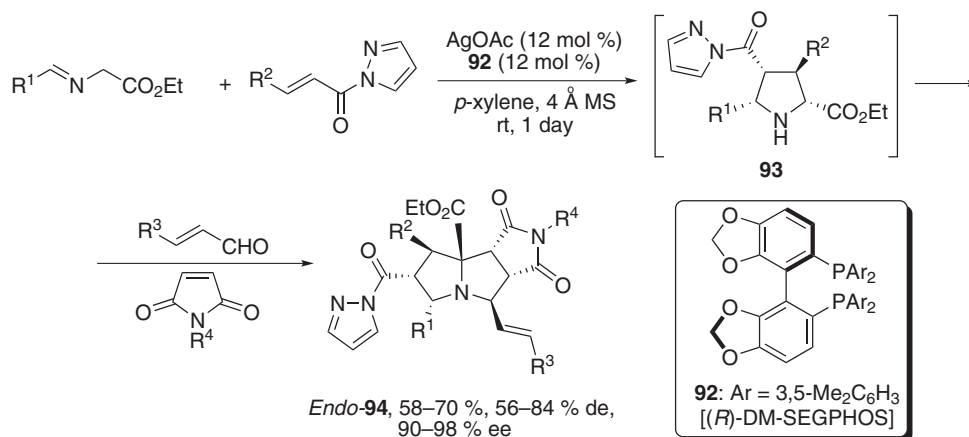


Fig. 7: Pyrrolizidines from *exo*-nitroprolinate **90** (R¹ = R² = Ph), cinnamaldehyde and dipolarophiles.

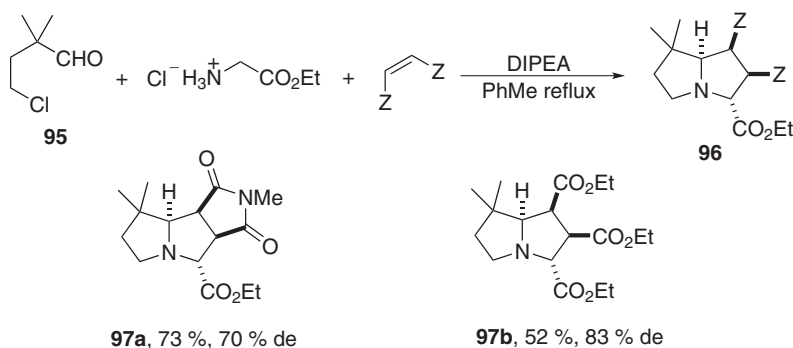


Scheme 16: Double consecutive 1,3-DC.

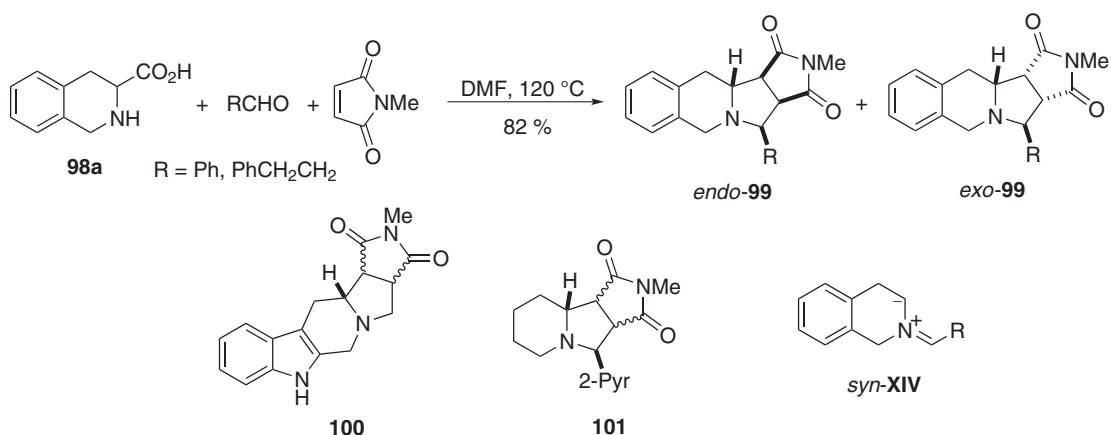
A different multicomponent 1,3-DC has been performed by Coldham and co-workers using the aldehyde **95**, glycine ethyl ester hydrochloride and dipolarophiles (Scheme 17) [63]. This process afforded pyrrolizidines **96** under refluxing toluene with good diastereoselectivity in favor of the *endo*-cycloadducts.

Multicomponent synthesis of indolizidines by decarboxylative 1,3-DC

The decarboxylative route to azomethine ylides from primary and secondary α -amino acids was first described by Grigg and co-workers [7–12]. Starting from tetrahydroisoquinoline-3-carboxylic acid **98a** and aldehydes and *N*-methylmaleimide in DMF at 120 °C, the corresponding cycloadducts **99** were obtained as *ca.* 1:1 mixture of *endo* and *exo*-benzoindolizidines **99** derived from the *syn*-dipole **XIV** (Scheme 18). This process has been studied with tetrahydro- β -carboline-3-carboxylic acid giving a 1:1 mixture of *endo*/*exo*-products **100**. In the case of pipercolinic acid the corresponding indolizidine **101** was formed by reaction



Scheme 17: Three-component 1,3-DC of chloro aldehyde **95** with ethyl glycinate and dipolarophiles.



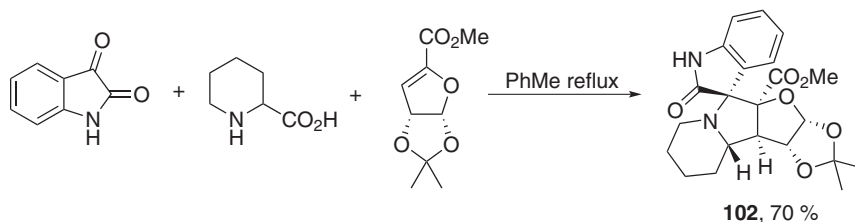
Scheme 18: Three-component 1,3-DC of tetrahydroisoquinoline-3-carboxylic acid, aldehydes and maleimides.

with 2-pyridinecarboxaldehyde and *N*-methylmaleimide (NMM) in 70 % yield. However, in the case of tetrahydroisoquinoline- and tetrahydro- β -carboline-1-carboxylic acid the reaction with benzaldehyde and NMM gave, through *syn* and *anti*-dipoles, mixtures of the four diastereomers.

Grigg and co-workers also demonstrated that, in the case of cyclic α -amino acids intermediate oxazolidine-5-ones, 1,4-prototropic rearrangement of the azomethine ylide or formation of a stable azomethine ylide can occur during the decarboxylative 1,3-DC [10, 64].

Banerjee and co-workers studied the reaction of pipecolic acid with isatin and a carbohydrate olefin (Scheme 3) [17]. In the case of pipecolic acid the spiro compound was formed under refluxing toluene (Scheme 19).

Other examples using isatins, already described in the case of pyrrolizidines, are compiled in Fig. 8 using pipecolic acid. In these cases, compound **103** has been isolated by a three-component 1,3-DC using an unsaturated carbohydrate lactone as dipolarophile [24]. Another example is the synthesis of spiro indolizidines **104** from nitro chromans **22** [25]. In the reaction of tetraethyl vinylidenebis(phosphonate) (**38**) [25] the



Scheme 19: Three-component 1,3-DC of pipecolic acid, isatin and a carbohydrate-derived dipolarophile.

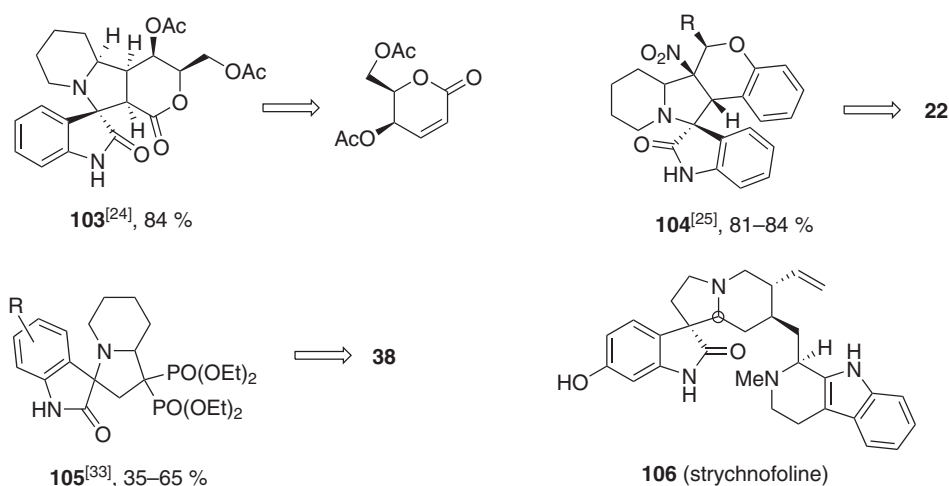
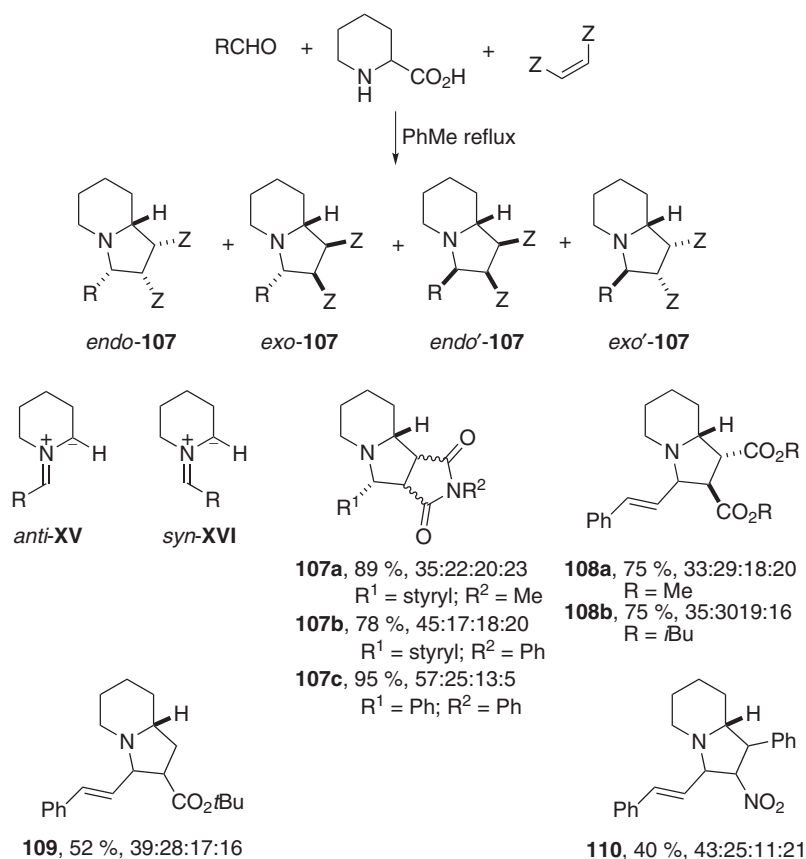


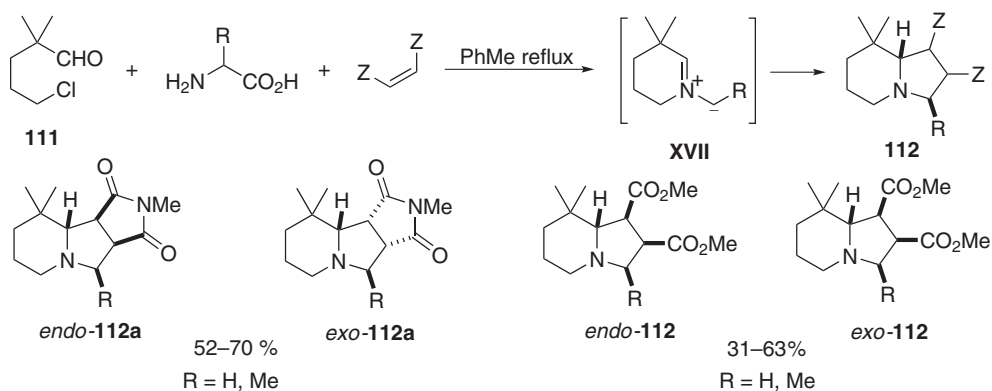
Fig. 8: Spirooxindole-indolizidines.

corresponding indolizidines **105** were prepared in acetonitrile at 80 °C in moderate yields. This spiro indole-indolizidine unit is present in the natural product strychnofoline **106**.

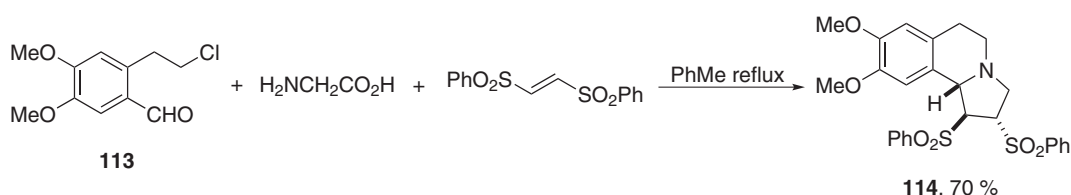
Our group has studied the multicomponent decarboxylative 1,3-DC of pipecolic acid with cinnamaldehyde or benzaldehyde with different dipolarophiles providing indolizidines **107** (Scheme 20) [65]. The process took place in refluxing toluene giving mixtures of the four diastereomers due to the participation of *anti*- and *syn*-**XVII** azomethine ylides. In the case of NMM or NPM products **107a–c** were formed whereas



Scheme 20: Three-component 1,3-DC of pipecolic acid, aldehydes and dipolarophiles.



Scheme 21: Three-component 1,3-DC of aldehyde **111** with α -amino acids and dipolarophiles.



Scheme 22: Three-component 1,3-DC of glycine, the aldehyde **113** and (*E*)-bis(phenylsulfonyl)ethylene.

dimethyl and diisobutyl fumarates afforded indolizidines **108a–b**. In the example of *tert*-butyl acrylate only regioisomeric products **109**, resulted from the α -attack of azomethine ylides **XV** and **XVI**, were isolated. The same happened with β -nitrostyrene, providing the nitroindolizidines **110**.

Coldham and co-workers have used **111**, the homologous aldehyde of **95** (Scheme 17), in the three-component decarboxylative 1,3-DC with α -amino acids and dipolarophiles, affording 1:1 mixtures of *endo:exo* indolizidines **112** under refluxing toluene, by intermediacy of the azomethine ylide **XVII** (Scheme 21) [63, 66].

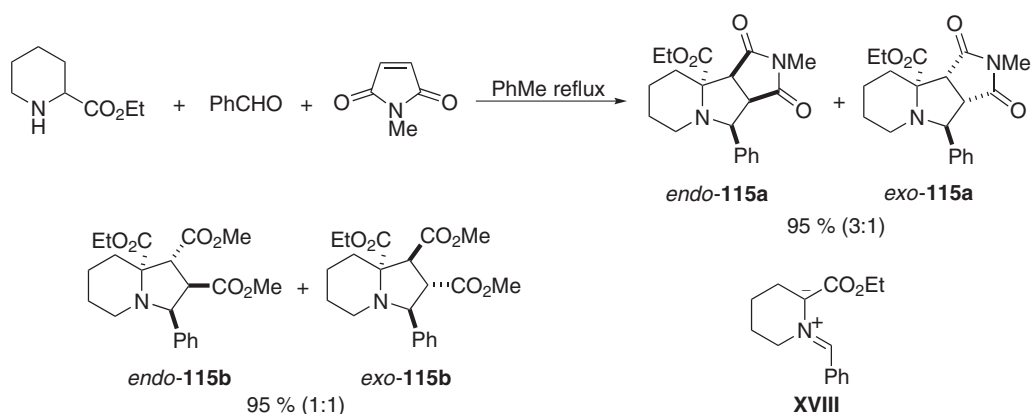
The former process has been performed with different halogen substituted aldehydes. In the case of *ortho*-2-(bromoethyl)benzaldehyde **113**, the precursor **114** of crispine was prepared in 70 % yield (Scheme 22) [66].

Multicomponent synthesis of indolizidines by 1,3-DC

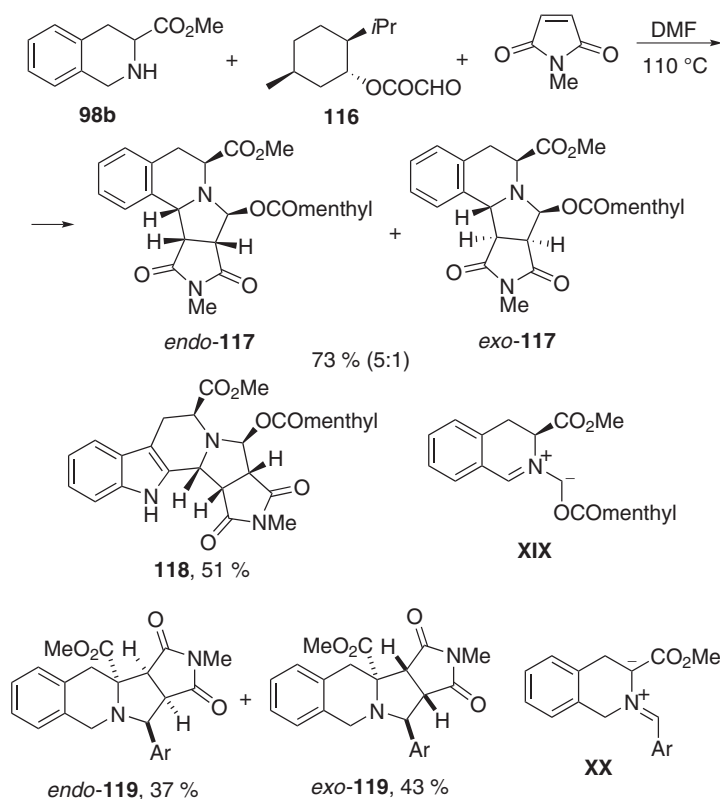
Joucla and co-workers reported the multicomponent 1,3-DC of ethyl pipercolinate with benzaldehyde and NMM giving a 3:1 mixture of *endo/exo* indolizidines **115a** (Scheme 23) [51]. However, in the case of methyl fumarate a 1:1 mixture of *endo/exo* **115b** was obtained. The diastereomeric result was explained by the participation of the azomethine ylide **XVIII**.

As in the case of alkyl prolinates, Grigg and co-workers described the three-component 1,3-DC of methyl tetrahydroisoquinoline-3-carboxylate (**98b**) with (+)-menthyl glyoxylate (**116**) and NMM [67]. This 1,3-DC took place in DMF at 110 °C providing a 5:1 mixture of *endo/exo* cycloadducts **117** in 73 % yield arising from the azomethine ylide **XIX** (Scheme 24). Methyl tetrahydro- β -carboline-3-carboxylate gave a 3.5:1 mixture of isomeric cycloadducts, compound **118** being isolated in 51 % yield. However, when 2-methoxybenzaldehyde was allowed to react with methyl tetrahydroisoquinoline-3-carboxylate a *ca.* 1:1 mixture of separable products **119** were obtained by the formation of the azomethine ylide **XX**.

Our group has described the three-component 1,3-DC of methyl pipercolinate hydrochloride with cinnamaldehyde and dipolarophiles, in toluene at 75 °C, affording indolizidines **120–127** as mixture of diastereomers (Scheme 25) [65]. In the case of methyl acrylate, *endo*-**120** was isolated in agreement with the α -attack of azomethine ylide **XXI**. Methyl fumarate gave a separable mixture of *endo/exo*-adducts **121** in 70 and 11 %



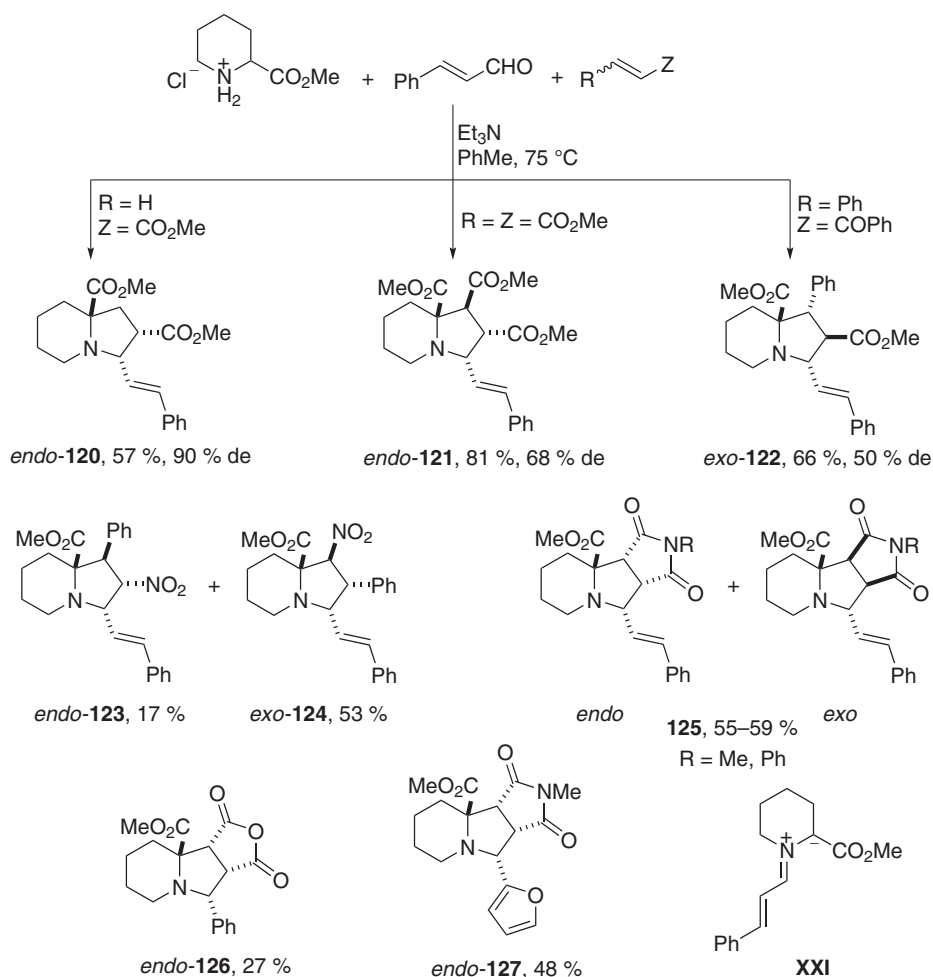
Scheme 23: Three-component 1,3-DC of ethyl prolinolate, benzaldehyde and dipolarophiles.



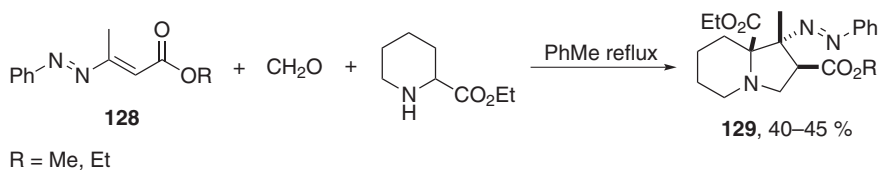
Scheme 24: Three-component 1,3-DC of methyl tetrahydroisoquinoline-3-carboxylate and methyl tetrahydro-β-carboline-3-carboxylate **98b** with (+)-menthyl glyoxylate **116** and dipolarophiles.

yield, respectively. However, chalcone afforded regioselectively *exo*-**122**. When β-nitro styrene was used as dipolarophile a 1:3 mixture of regioisomeric *endo*-**123** and *exo*-**124** was obtained. *N*-Methyl and *N*-phenylmaleimide gave a 7:3 mixture of products *endo/exo* **125**. When benzaldehyde was used as carbonyl component and maleic anhydride as dipolarophile, compound *endo*-**126** was obtained in modest yield with total diastereoselectivity. In the case of the reactions performed with furfural and NMM, products *endo/exo* **127** were isolated with 64 % de. The major *endo*-products could be isolated and in the case of *endo*-**127** the relative configuration was assigned according to X-ray diffraction analysis.

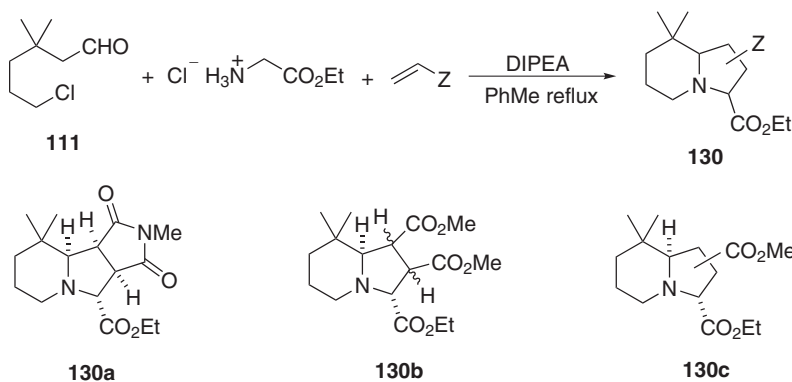
The multicomponent 1,3-DC of 1,2-diaza-1,3-diene **128** with formaldehyde and ethyl pipercolate gave regioselectively indolizidine derivatives **129** in moderate yield (Scheme 26) [68].



Scheme 25: Three-component 1,3-DC of methyl pipecolate with cinnamaldehyde and dipolarophiles.



Scheme 26: Three-component 1,3-DC of ethyl pipecolate, compounds 128 and formaldehyde.



Scheme 27: Three-component 1,3-DC of ethyl glycinate, the aldehyde 111 and dipolarophiles.

Coldham and co-workers have described the three-component 1,3-DC of the γ -chloro aldehyde **95** for the synthesis of pyrrolizidines (Scheme 17) [63]. When the homologous aldehyde **111** was allowed to react with ethyl glycinate hydrochloride and different dipolarophiles, indolizidines **130** were prepared (Scheme 27) [66]. In the case of NMM and methyl maleate, a mixture of three separable diastereomers in *ca.* 2:2:1 and 94 and 74 % yield were obtained, respectively, diastereomers **130a** and **130b** being mainly identified. For methyl acrylate, a 3.4:2.4 mixture of the corresponding regioisomers **130c** was obtained in 77 % overall yield.

Conclusions

Three-components 1,3-dipolar cycloadditions between cyclic α -amino acids, carbonyl compounds and electrophilic alkenes are an excellent, simple and powerful methodology for the thermal synthesis of the pyrrolizidine and indolizidine derivatives. The atom economy of these processes is total except for the reactions involving decarboxylations where a small molecule of carbon dioxide is lost. By means of proline and pipercolinic acid or related amino acids the intermediate azomethine ylides are formed by condensation with the carbonyl compound via a decarboxylative process. This methodology allows the synthesis of spiro-pyrrolizidines and -indolizidines when ketones are used as carbonyl component with high regio- and diastereo-control. In particular, the synthesis of biological active spirooxindole-pyrrolizidines can be carried out using isatins as carbonyl components in only one step operation. The regio- and diastereoselectivity can be better controlled in the case of using cyclic α -amino acid derived esters than in the decarboxylative 1,3-DC giving the corresponding pyrrolizidines and indolizidines with an alkoxycarbonyl substituent in the bridge of the bicyclic systems. The last methodology can be also performed using a double 1,3-DC, first the asymmetric synthesis of the proline unit followed by the three-component 1,3-DC affording enantioenriched pyrrolizidines.

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